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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/073,077	02/12/2002	Thomas R. Gadek	9491-058-27	3125

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EXAMINER	
COUNTS, GARY W	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 07/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/073,077	GADEK ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25 and 27-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25, 27-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

The amendment filed 05/22/06 is acknowledged and has been entered.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 25, and 27-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 the recitation "wherein the member of the first set of ligands and the member of the second set of ligands do not have all the same functional groups" is vague and indefinite because it is unclear what function groups applicant is referring to on the first and second set of ligands. Does applicant intend functional groups which bind to the target biomolecule? Does applicant intend functional groups of the first and second set of ligands which provides for the linking of a first ligand to a second ligand or does applicant intend something else? Please clarify.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 25, 28, 30, 31 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffey et al. (US 6,770,486) in view of Hadjuk et al (Discovery of Potent Nonpeptide Inhibitors of Stromelysin Using SAR by NMR, J. Am. Chem. Soc. 1997, 119, 5818-5827).

Griffey et al disclose methods of identifying compounds that bind to a target of interest. Griffey et al disclose sets of ligands that are screened to determine ligands that non-covalently bind to a target molecule. Griffey et al disclose selecting ligands from the sets and chemically linking the ligands to form a compound. Griffey et al

disclose that the two ligands can be concurrent ligands which bind to distinct sites on the target molecule. Griffey et al disclose that the compound formed by linking the first ligand and second ligand has a greater affinity for the target molecule than either first or second ligand (abstract, col 5, lines 21-29, col 7, & col 23). Griffey et al disclose detecting the binding of the compound to the target molecule by mass spectrometery. Griffey et al disclose that the target molecule can be proteins (col 6, col 8, col 15). Griffey et al disclose that the linked ligands can be screened in the same manner as were the parent ligands (col 24) and also teaches they can be screened one at a time (col 17). Griffey et al disclose that the interactions between the ligands and the target biomolecules can be hydrogen-bonding, electrostatic and hydrophobic contacts (col 8 and col 16).

Griffey et al differ from the instant invention in failing to specifically teach the first set of ligands and the member of the second set of ligands do not have all the same functional groups.

Hajduk et al disclose ligands that have functional groups and discloses that different ligands are linked together to form linked compounds that bind to a protein. Hajduk et al disclose that one of the ligands can be acetohydroxamic acid (same as used by applicant on page 44) and also discloses second ligands which bind to a second different site such as the ligands disclosed in table 1, page 5819 (it is noted that the ligands 6, 8, 9 and 11 are the same as the ligands 7B, 7A, 7C and 7E respectively as disclosed by applicant on page 42 of the specification). Hajduk et al disclose that the protein can be stromelysin. Hajduk et al discloses that the combination of the ligands

provides for high affinity ligands for proteins and when applied to protein drug targets provides and extremely valuable tool in drug research (p. 5822-5823).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate ligands and proteins such as taught by Hajduk et al into the method of Griffey et al because Griffey et al is generic with respect to the ligands that bind to proteins and one would use the appropriate reagent, i.e. ligands to detect the desired analyte, in this case proteins. Further, the combination of Griffey et al and Hajduk et al disclose the same ligands has disclosed by applicant. Therefore, the modified method of Griffey et al would comprise first and second ligands linked together which do not have all the same functional groups. Further, Hajduk et al teaches that the combination of the ligands provides for high affinity ligands for proteins and when applied to protein drug targets provides and extremely valuable tool in drug research.

With respect to the recitation "identifying a 1:1 complex of linked ligand compound and target biomolecule" as recited in the instant claims. Griffey et al disclose that the linked ligands can be screened in the same manner as were the parent ligands (col 24) and also teaches they can be screened one at a time. Therefore, Griffey et al is teaching identifying a 1:1 complex of linked ligand compound and target biomolecule.

7. Claims 27 and 29 and rejected under 35 U.S.C. 103(a) as being unpatentable over Griffey et al and Hajduk et al in view of Wells et al (WO 00/00823).

See above for the teachings of Griffey et al and Hajduk et al.

Griffey et al and Hajduk et al differ from the instant invention in failing to specifically teach the first binding site is the same as the second binding site. Griffey et al also fail to specially teach the disassociation constant equal to 500 uM or less.

Wells et al disclose two ligands linked together to bind to two binding sites on a target biomolecule (p. 22). Wells et al disclose that these ligands have non-covalent affinity for the site of interest (p. 15). Wells et al disclose that linked ligands can bind to the target biomolecule comprising two binding sites that are the same. Wells e al discloses that each member of the linked conjugate can be from the same class.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use linked ligands comprising ligands from the same class to bind to two sites on a target biomolecule that are the same because Wells et al shows that target biomolecules comprise two sites that are the same and Wells et al shows that using ligands from the same class allows for linked ligands that have non-covalent affinity for the site of interest and thus allows for new small drug leads (p. 3).

With respect to the dissociation constant as recited in the instant claims. Although Griffey et al fails to specifically teach the disassociation constant equal to 500 uM or less. Griffey et al does disclose that that the selection of a dissociation constant is compared to a standard and selected accordingly (col 16). The optimal dissociation constant of the ligands can be determined by routine experimentation and thus would have been obvious to one of ordinary skill in the art. Further, it has long been settled to be no more than routine experimentation for one of ordinary skill in the art to discover an optimum value of a result effective variable. "[W]here the general conditions of a claim are disclosed in the prior art, it is

not inventive to discover the optimum of workable ranges by routine experimentation." Application of Aller, 220 F.2d 454,456, 105 USPQ 233, 235-236 (C.C.P.A. 1955). "No invention is involved in discovering optimum ranges of a process by routine experimentation ." Id. At 458,105 USPQ at 236-237. The "discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." Application of Boesch, 617 F.2d 272,276, 205 USPQ 215, 218-219 (C.C.P.A. 1980).

8. Claims 31 and 32 rejected under 35 U.S.C. 103(a) as being unpatentable over Griffey et al and Hajduk et al in view of Ellman (WO 99/49314).

See above for the teachings of Griffey et al and Hajduk et al.

Griffey et al and Hajduk et al differ from the instant invention in failing to specifically teach the protein is a cytokine receptor such as erythropoietin.

Ellman disclose the use of erythropoietin (p. 17) to determine if crosslinked ligands bind to erythropoietin.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use erythropoietin as a target molecule as taught by Ellman into the method of Griffey et al because Griffey et al is generic with respect to the protein target molecule to be used to determine binding ligands and one would use the appropriate reagent, i.e. erythropoietin to determine the desired binding ligands, in this case ligands which bind to erythropoietin.

9. Claims 31 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffey et al and Hajduk et al in view of Erlanson et al (US 6,919,178).

See above for the teachings of Griffey et al and Hajduk et al.

Griffey et al and Hajduk et al differ from the instant invention in failing to specifically teach the protein is protein tyrosine phosphatase 1b (PTP1b).

Earlson et al disclose target biomolecules which can be used to determine ligands which can bind to sites on the target biomolecule. Earlson et al disclose that the target biomolecule can be protein tyrosine phosphatases such as PTP1b.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use PTP1b as a target molecule as taught by Earlson et al into the modified method of Griffey et al because Griffey et al is generic with respect to the protein target molecule to be used to determine binding ligands and one would use the appropriate reagent, i.e. PTP1b to determine the desired binding ligands, in this case ligands which bind to PTP1b.

Response to Arguments

10. Applicant's arguments filed 05/22/06 have been fully considered but they are not persuasive.

112 2nd rejection

Applicant states that the term "functional group" is believed clear on its face and that the term "functional group" is well known in the art as applied to a molecule such as the ligands described in claim 25. This is not found persuasive because the Examiner has not said that the term "functional group" is vague and indefinite but rather has indicated that it is unclear from the claim what functional group applicant is referring to on the first and second set of ligands. Applicant argues that as to the functional groups which bind to the target biomolecule or provide for linking between the first and second

ligands, the applicant is not to be construed. This is not found persuasive because the claims must stand on their own merits and it is unclear for the claim language what applicant intends. Applicant further states that Exemplary functional groups are described in the specification and directs Examiner's attention to page 25, lines 6-10. This is not found persuasive because the claims are read in light of the specification and the claims as currently recited are unclear for reasons stated above and in the previous office action.

103 rejections

Applicant argues that Griffey does not teach identifying a 1:1 complex of parent ligand binding to a target. This is not found persuasive because as stated in the previous office action the linked ligands can be screened in the same manner as were the parent ligands (col 24) and also teaches they can be screened one at a time (see col 17). Therefore, Griffey is teaching that the parent ligands were determined by determining the binding of one parent ligand with a target and since Griffey teaches that the linked ligands can be screened in the same manner as the parent ligands, one of ordinary skill in the art would recognize that Griffey et al is also teaching one linked ligand with a target.

Applicant argues that Griffey is defective as prior art reference for the purposes of enabling that target molecule can be proteins, teaching ligands with the functional groups of the present claim 25 and teaching ligands that have different functional groups. This is not found persuasive because as stated in the previous office action Griffey et al specifically teaches that the target molecule can be proteins (col 6, col 8,

col 15). Second, MPEP 2121 states that when the reference relied upon expressly anticipates or makes obvious all of the elements of the claimed invention, the reference is presumed to be operable. Once such a reference is found, the burden is on applicant to provide **facts** rebutting the presumption of operability. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). Finally, Applicant's argument consist of arguments of counsel which cannot take the place of factual evidence (see MPEP 2145). Further as stated above it is unclear what functional groups applicant is referring to (see 112 2nd rejection above). Also, with respect to the ligands Applicant is arguing the references individually. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Applicant argues that there is no motivation to combine Griffey and Hajduk. This is not found persuasive because as stated above It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate ligands and proteins such as taught by Hajduk et al into the method of Griffey et al because Griffey et al is generic with respect to the ligands that bind to proteins and one would use the appropriate reagent, i.e. ligands to detect the desired analyte, in this case proteins. Further, the combination of Griffey et al and Hajduk et al disclose the same ligands has disclosed by applicant. Therefore, the modified method of Griffey et al would comprise first and second ligands linked together which do not have all the same functional

groups. Further, Hajduk et al teaches that the combination of the ligands provides for high affinity ligands for proteins and when applied to protein drug targets provides and extremely valuable tool in drug research. Thus, one of ordinary skill in the art would have a reasonable expectation of success incorporating ligands such as taught by Hajduk et al into the method of Griffey et al to bind to a protein of interest.

Applicant argues that Griffey et al combined with Wells does not teach all the elements. This is not found persuasive because of reasons of record and as stated above it is the Examiner's position that Griffey et al is enabled and the combination with the secondary and tertiary references is considered appropriate because the secondary and tertiary references teach the desired advantages for combining. Thus, it is the Examiner's position that the combined references read on the instantly recited claims.

Applicant argues that the tertiary references of Ellam or Erlanson combined with Griffey et al does not teach all of the elements. This is not found persuasive because as stated above the combination of Griffey et al and Hadjuk et al is reads on the elements Applicant is referring to and thus the combination of the tertiary references with Griffey et al and Hadjuk et al is considered appropriate and reads on the instantly recited claims.

Conclusion

11. No claims are allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art Unit 1641
July 20, 2006

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